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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

DEVI, SARVAMANGALA J N

ART UNIT	PAPER NUMBER
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1645

DATE MAILED: 07/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action

Application No.

09/701,453

Applicant(s)

GRANOFF ET AL.

Examiner

S. Devi, Ph.D.

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--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

- a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
- b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on 01 June 2004. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☐ The proposed amendment(s) will not be entered because:
- (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);
- (b) ☐ they raise the issue of new matter (see Note below);
- (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
- (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____

3. ☐ Applicant's reply has overcome the following rejection(s): _____.
4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Attachment.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: None.

Claim(s) objected to: None.

Claim(s) rejected: 17-28.

Claim(s) withdrawn from consideration: 29.

8. ☐ The drawing correction filed on _____ is a) ☐ approved or b) ☐ disapproved by the Examiner.
9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____.
10. ☒ Other: Attachment & PTO 892.

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ATTACHMENT TO ADVISORY ACTION

- 1) Acknowledgment is made of Applicants' after-final amendment filed 06/01/04 in response to the final Office Action mailed 12/03/03.

Status of Claims

- 2) Claims 17, 19, 20, 22, 24, 26 and 28 have been amended via the amendment filed 06/01/04.
Claims 17-29 are pending.
Claims 17-28 are under examination.

Prior Citation of Title 35 Sections

- 3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

- 4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

- 5) The objection to the specification made in paragraph 6 of the Office Action mailed 03/20/03 and maintained in paragraph 6 of the Office Action mailed 12/03/03 with regard to the trademark recitations is withdrawn in light of Applicants' amendments to the specification.

Rejection(s) Withdrawn

- 6) The rejection of claims 24 and 28 made in paragraph 9 of the Office Action mailed 12/03/03 under 35 U.S.C. § 112, first paragraph, as containing new subject matter, is withdrawn in light of Applicants' amendments to the claims.
- 7) The rejection of claim 17 made in paragraph 10(a) of the Office Action mailed 12/03/03 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.
- 8) The rejection of claim 26 made in paragraph 10(b) of the Office Action mailed 12/03/03 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.
- 9) The rejection of claim 26 made in paragraph 10(c) of the Office Action mailed 12/03/03

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under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

10) The rejection of claim 19 made in paragraph 10(d) of the Office Action mailed 12/03/03 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

11) The rejection of claim 22 made in paragraph 10(e) of the Office Action mailed 12/03/03 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

12) The rejection of claim 22 made in paragraph 10(f) of the Office Action mailed 12/03/03 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

13) The rejection of claims 18-25 made in paragraph 10(g) of the Office Action mailed 12/03/03 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

Rejection(s) Maintained

14) The rejection of claims 17-23 and 25 made in paragraph 11 of the Office Action mailed 12/03/03 under 35 U.S.C § 103(a) as being unpatentable over Costantino *et al.* (*Vaccine* 10: 691-698, 1992 - already of record) and van der Voort *et al.* (*Infect. Immun.* 64: 2745-2751, 1996) in view of Paradiso *et al.* (*Dev. Biol. Stand.* 87: 269-275, 1996), is maintained for reasons set forth therein and herebelow. See paragraph below.

15) The rejection of claim 24 made in paragraph 12 of the Office Action mailed 12/03/03 under 35 U.S.C § 103(a) as being unpatentable over Costantino *et al.* (*Vaccine* 10: 691-698, 1992 - already of record) as modified by van der Voort *et al.* (*Infect. Immun.* 64: 2745-2751, 1996) and Paradiso *et al.* (*Dev. Biol. Stand.* 87: 269-275, 1996) as applied to claim 17 above, and further in view of Granoff (US 6,413,520, already of record) ('520), is maintained for reasons set forth therein and herebelow.

Applicants point to section 2142 of the MPEP and list the basic requirements for *prima facie* obviousness, i.e.,: a) some suggestion or motivation to modify the references or combine reference teachings; b) a reasonable expectation of success for the modification; and c) the prior art references

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teaching or suggesting all of the claim limitations. Applicants state that the teaching or suggestion and the reasonable expectation of success must both be found in the prior art, not in Applicants' disclosure. Applicants allege that these criteria have not been satisfied. Applicants submit that there is no motivation to modify the references and that there is no reasonable expectation of success regarding the use of combination vaccines as claimed. Applicants contend that none of the cited art, either alone or in combination, teaches or suggests the claimed combination. Applicants acknowledge that Costantino teaches a meningococcus A and C conjugate vaccine, but state that Costantino teaches away from the claimed invention. Applicants submit that Costantino *et al.* do not describe or suggest using the meningococcus A and C conjugate vaccine with an NmB protein, let alone an NmB proteoliposomic vesicle preparation. Applicants cite a passage from page 691 of Costantino *et al.* and state that Costantino *et al.* do not suggest combining a conjugated NmC oligosaccharide with an NmB component, especially an NmB component provided as proteoliposomic vesicles.

Applicants submit that van der Voort *et al.* teach a hexavalent vaccine made from six engineered strains of NmB, but do not discuss or suggest the use of the NmB vaccine with other meningococcal serogroups, such as NmC, and do not provide motivation to combine the conjugated NmC oligosaccharide with NmB proteoliposomic vesicles.

With regard to the teachings of Paradiso, Applicants contend that Paradiso does not provide the motivation to combine the teachings of Costantino and van der Voort. Applicants allege that the Office has completely taken out of context the passage from the bridging paragraph at pages 272 and 273. Applicants state that the sentence reads as follows:

Since these vesicle preparations contain an array of potential and lipids, the combinations will create a new set of formulation **challenges not unlike those encountered in mixing conjugate vaccines with DTP.**
[Emphasis in original].

Applicants further allege that the Office has left off the salient part of the sentence, shown in bold, when quoting the passage. Applicants opine that Paradiso bolsters the patentability of the present claims by acknowledging that the preparation of combination vaccines is not a straight-forward task, without potential problems.

Applicants' arguments have been carefully considered, but are non-persuasive. As set forth

previously, the Office has established a *prima facie* case of obviousness. All the three basic requirements for *prima facie* obviousness listed in section 2142 of the MPEP are met: a) suggestion and motivation to modify the references or combine reference teachings; b) a reasonable expectation of success for the modification; and c) the prior art references teaching or suggesting all of the claim limitations.

If Costantino *et al.* taught all the ingredients of the claimed composition, then the reference of Costantino *et al.* would have been used as an anticipatory prior art under 35 U.S.C § 102. As opposed to teaching away from the instant invention, Costantino taught one of the active ingredients of the instantly claimed composition, i.e., group A and/or C glycoconjugate. van der Voort taught the other active ingredient of the instantly claimed composition, i.e., B-OMV. The motivation to combine Costantino's group C meningococcal oligosaccharide-CRM197 conjugate with van der Voort's immunogenic group B meningococcal hexavalent outer membrane vesicle vaccine comes from the explicit teaching of or suggestion by Paradiso *et al.*

Contrary to Applicants' argument, Paradiso *et al.* do provide the motivation to combine the immunogenic components from Costantino and van der Voort. Paradiso *et al.* taught that they have prepared immunogenic glycoconjugates of group C meningococcal saccharides covalently linked to the carrier CRM₁₉₇ which elicited a booster response characteristic of a T-dependent response in humans. Paradiso *et al.* further taught that since group B meningococcal capsule is not very immunogenic in people, the alternative approach of using outer membrane vesicles from a virulent group B meningococcal strain has been sought (see page 272). The full passage bridging pages 272 and 273 of Paradiso *et al.* is provided below, with the relevant salient portion highlighted in bold (see paragraph bridging pages 272 and 273):

A significant portion of the morbidity from meningococcus is caused by group B. Unfortunately, the capsule from group B is not very immunogenic in people because of the similarity to saccharide structures on human cells. For this reason, and because of the potential for anti-group B antibody to cross-react with brain tissue, alternative approaches have been sought. **Most of the work has been done on outer membrane vesicles prepared from cells of virulent group B strains [10]. It seem likely that in the future it will be desirable to mix such a vaccine with the group C and/or group A conjugates.** Since these vesicle preparations contain an array of proteins and lipids, the combinations will create a new set of formulation challenges not unlike those encountered in mixing conjugate vaccines with DTP. [Emphasis added].

The key teaching or suggestion relevant to the instant rejection expressly taught by Paradiso *et al.* and specifically left out by Applicants is separated from Paradiso's passage above and is re-cited

below for Applicants' attention:

Most of the work has been done on **outer membrane vesicles** prepared from cells of virulent group B strains [10]. It seem likely that **in the future it will be desirable to mix such a vaccine with the group C and/or group A conjugates**. [Emphasis added].

Thus, contrary to Applicants' allegation, both the teaching or suggestion and the reasonable expectation of success are found in the prior art, and did not come from Applicants' disclosure. With the Costantino's group A and/or C glycoconjugate and van der Voort's group B meningococcal OMV known and available in the art, and given the express teaching or suggestion by Paradiso *et al.* that 'in the future it will be desirable to mix such a vaccine, i.e., outer membrane vesicles prepared from cells of virulent group B strains, with the group C and/or group A conjugates', one of skill in the art would have readily understood the desirability for 'mixing' Costantino's group C and/or group A glycoconjugate with van der Voort's group B meningococcal outer membrane vesicles.

With regard to the alleged lack of reasonable expectation of success, the fact that experimentation may not be straight-forward or may be complex does not necessarily equate the experimentation taught or suggested by the prior art to be undue. Such a prior art reference cannot be dismissed as one that teaches away from the invention. In the instant case, the experimentation is well within the realm of routine experimentation because the art typically engages in such experimentation. In response to Applicants' argument that there is no suggestion to combine the teachings of the references, the Office recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the *knowledge generally available to one of ordinary skill in the art*. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The state of the art at the time documented the following to be known in the art:

(A) In 1994, Corbel (*Biologicals* 22: 353-360, 1994) taught that the 'concept of combined vaccines is not novel'. Corbel expressly taught that the pharmacopoeial requirements for each combination will have to be assessed on a case-by-case basis (see paragraph bridging pages 353 and 354). With specific reference to the claimed immunogenic composition, Corbel expressly taught

combining a vaccine composition comprising a group C meningococcal conjugate with 'B-OMV' (see Table 1; Figure 2; and paragraph bridging pages 358 and 359). Although Corbel speculated that a formulation of increasingly complex vaccine combinations may present some potential problems, Corbel expressly taught that potential sub-optimal antibody responses, antigenic competition, or epitope suppression may have to be detected by careful monitoring of vaccinees. Corbel expressly taught that these effects may be dose- or schedule-dependent and thus 'amenable to management' (see paragraph bridging pages 359 and 360), thereby indicating the experimentation to be extensive or complex, but routine, manageable, and well within the realm of what one of skill in the art usually engages in.

(B) With special reference to the combining of meningococcal porin proteosomes to a composition comprising a group C meningococcal polysaccharide linked to a carrier, such as a lipid, the state of the art demonstrated no potential problems. The meningococcal OMP proteosomes were well known in the art to serve as excellent immunopotentiating adjuvants when combined with a group C meningococcal polysaccharide linked to a lipid carrier. For example, Wetzler (*Ann. N.Y. Acad. Sci.* 730: 367037, 1994) showed that combining meningococcal OMP proteosomes with a group C meningococcal capsular polysaccharide linked to a lipid carrier was straight forward and routine. The meningococcal OMP proteosomes in the combined vaccine served as excellent immunopotentiating agents, i.e., adjuvants. See entire publication of Wetzler. Given Wetzler's demonstration that the meningococcal OMP proteosome has excellent immunopotentiating properties and serves as an effective adjuvant for the polysaccharide component in a vaccine, one of skill in the art would have had a reasonable expectation of success in combining Costantino's vaccine comprising group A and C meningococcal oligosaccharide-CRM197 conjugate with van der Voort's group B meningococcal OMV.

In sum, Applicants appear to argue that the combination of references fails because the prior art does not have anticipatory references regarding all elements of the invention. The argument is not persuasive. It should be noted that what would reasonably have been known and used by one of ordinary skill in the art need not be explicitly taught. See *In re Nilssen*, 851 F.2d 1401, 7 USPQ2d 1500 (Fed. Cir. 1988). The test of obviousness is not express suggestion of the claimed invention in any and all of the references, but rather what the references taken collectively would reasonably have

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suggested to those of ordinary skill in the art presumed to be familiar with them. *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981). In the instant case, there is express suggestion provided by Paradiso *et al.* to mix group B meningococcal outer membrane vesicles with a group C and/or A conjugate. Obviousness does not require absolute predictability, (see *In re Lamberti*, 192 USPQ 278), but only a reasonable expectation of success (see *In re O'Farrell*, 7 USPQ 2d 1673, Fed. Cir. 1988), which has been established.

The art rejections stand. Although Corbel qualifies as an alternate secondary reference by providing the same motivation as the one provided by Paradiso *et al.* both Corbel and Wetzler are cited herein solely for rebutting Applicants' arguments and to document the state of the art at the time of the invention.

Remarks

16) Claims 17-28 stand rejected.

17) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

18) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.Mov>. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

19) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system. A message may be left on the Examiner's voice mail system.

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If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

July, 2004


S. DEVI, PH.D.
PRIMARY EXAMINER